Preoperative ketamine administration for prevention of postoperative neurocognitive disorders after major orthopedic surgery in elderly patients: A multicenter randomized blinded placebo-controlled trial

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Running title: The POCK Randomized Clinical Trial

Abstract

Background: Preventive anesthetic impact on the high rates of postoperative neurocognitive disorders in elderly patients is debated. The Prevention of postOperative Cognitive dysfunction by Ketamine (POCK) study aimed to assess the effect of ketamine on this condition.

Methods: This is a multicenter, randomized, double-blind, interventional study. Patients ≥60 years undergoing major orthopedic surgery were randomly assigned in a 1:1 ratio to receive preoperative ketamine 0.5 mg/kg as an intravenous bolus (n=152) or placebo (n=149) in random blocks stratified according to study site, preoperative cognitive status and age. Primary outcome was proportion of objective delayed neurocognitive recovery (dNR) defined as a decline of one or more neuropsychological assessment standard deviations on postoperative day 7. Secondary outcomes included three-month incidence of objective postoperative neurocognitive disorder (POND), as well as delirium, anxiety, and symptoms of depression seven days and three months after surgery.

Results: Among 301 patients included, 292 (97%) completed the trial. Objective dNR occurred in 50 (38.8%) patients in the ketamine group and 54 (40.9%) patients in the placebo group (OR [95% CI] 0.92 [0.56;1.51], p=0.73) on postoperative day 7. Incidence of objective POND three months after surgery did not differ significantly between the two groups nor did incidence of delirium, anxiety, apathy, and fatigue. Symptoms of depression were less frequent in the ketamine group three months after surgery (OR [95%CI] 0.34 [0.13-0.86]).

Conclusions: A single preoperative bolus of intravenous ketamine does not prevent the occurrence of dNR or POND in elderly patients scheduled for major orthopedic surgery. (Clinicaltrials.gov NCT02892916.)

Keywords: Delayed neurocognitive recovery, Postoperative neurocognitive disorder, Ketamine, Frailty, Orthopaedic Surgery

Introduction

With a foreseeable world increase of 2.1 billion people aged 60 years or more by 2050, the prevalence of surgical procedures in the elderly is expected to increase up to fourfold in the next 40 years[1], especially in orthopedic surgery. However, elderly patients undergoing these procedures develop cognitive dysfunction after surgery in 26% to 54% of cases [2,3]. This includes impairments in verbal and visual memory, language comprehension, spatial abstraction, attention, and concentration. New recommendations based on the Diagnostic and Statistical Manual for Mental Disorders, fifth edition (DSM-5) distinguish three temporal categories of postoperative neurocognitive disorder: *acute postoperative events*, also called delirium, *delayed neurocognitive recovery* (dNR) that occurs within the first 30 days after the procedure and *postoperative neurocognitive disorders* (POND) that persist for up to 12 months [4]. Delayed neurocognitive recovery is associated with increased mortality, earlier retirement, and more frequent need for social assistance[5,6]. It is of upmost importance to identify the patients most at risk and find novel preventive interventions that minimize cognitive dysfunction after surgery[7].

A neuroinflammatory process, driven by microglial cells, is considered one of the major pathophysiological mechanisms of postoperative cognitive decline [8]. Among the various pharmacological agents having a direct and indirect microglial effect, ketamine, a non-competitive glutamate N-methyl-D-aspartic acid (NMDA) receptor antagonist with anti-inflammatory properties, is a very promising molecule[9]. Subanesthetic administration of ketamine reduces postoperative markers of inflammation [10], postoperative pain and opioid consumption[11], and has been studied in diseases where microglial cell activation plays a crucial role [9,12].

A meta-analysis has indicated that a single bolus of ketamine, administered at the onset of anesthesia, can decrease the risk of neurocognitive disorders up to 7 days after surgery [13]. Conversely, a large multicenter randomized clinical trial found this regimen ineffective in preventing acute postoperative cognitive dysfunction, i.e. delirium [14]. In addition, the hypothesis of a common physiological

substratum between postoperative delirium and POND has been recently challenged[15]. Our multicenter, randomized trial aimed to clarify these contradictory findings by determining whether ketamine, administered at anesthesia induction, could reduce the rates of dNR on postoperative day 7 (primary outcome). Additionally, we sought to assess its impact on the incidence of POND on postoperative day 90, along with anxiety, symptoms of depression, delirium, pain levels, and opioid use both on postoperative day 7 and day 90 (secondary outcomes). This assessment was conducted within in a homogenous surgical population, i.e. elderly patients undergoing major orthopedic surgery, where significant data regarding cognitive outcomes is particularly scarce.

Patients and Methods

Trial design and ethics statements

The POCK study was a multicenter, randomized, placebo-controlled, double-blind, superiority trial comparing ketamine with placebo in patients considered at risk of cognitive disorders after major orthopedic surgery. It was conducted in accordance with the declaration of Helsinki and was registered in September 2016 (clinicaltrial.gov NCT02892916). It was approved in June 2016 by an institutional review board (Comité de Protection des Personnes Ile de France III, David Simhon, 06/17/2016, France - #2016-000691-16) and the French National Agency of Medicine and Health Products Safety. Written and signed consent was obtained for all patients. The protocol, including the statistical analysis plan, is available with the full text of this article at the journal website. The members of the steering committee (see Table S1) designed the trial, gathered, and analyzed the data, and vouch for the accuracy and completeness of the data and analyses and the fidelity of the study to the protocol.

Participants

Fourteen French university and non-university hospitals took part in the trial (see Table S2). Patients aged 60 years and older were eligible for enrolment if they were competent to provide informed consent and were scheduled to undergo major orthopedic surgery under general anesthesia (e.g., spinal surgery including spinal decompression, hip or knee total joint arthroplasty, hip internal fixation, shoulder arthroplasty). Potential patients were identified by the local clinical team. Patients were not eligible if they had American Society of Anesthesiology (ASA) score > 4, emergency surgery (i.e., emergency hip fracture) or an expected length of stay in hospital < 48 hours, a known allergy or contraindication to ketamine, severe auditory or vision disorders, drug misuse history or chronic anti-psychotic medications, a severe alcohol liver disease (TP<50% and/or bilirubin > 50 µmol/L) or were not French speaking.

Randomization and masking

Patients underwent randomization between 03/20/2017 and 05/28/2019 and were assigned in a 1:1 ratio by means of a Web-based service to receive ketamine or placebo in random blocks of size 2 and 4 stratified according to study site, preoperative cognitive status defined by the Montreal Cognitive Assessment (MoCA) score (less than 20, considered as severe cognitive impairment, between 20 and 26, considered as mild cognitive impairment [MCI] and 26 or greater, considered as normal) and age (> 70 years *versus* ≤ 70 years) which are factors suspected to influence cognitive outcomes[3,16–18]. Prepared solutions of ketamine or placebo were directly delivered to the operating room in 10 ml syringes labelled with a randomization number and injected after induction of anesthesia. The study syringes were prepared by a non-attending nurse such that the contents were indiscernible. Treatment assignments were concealed from patients, physicians, research staff, the statistician, and the scientific committee. Quality control visits were periodically conducted at reach site during the study.

Trial procedures

Patients were assigned to receive either 0.5 mg/kg of intravenous ketamine (Ketamine Panpharma 50 mg/5 ml, Luitré, France) or an equivalent volume of placebo (sodium chloride 0.9%/5 mL vials, Chaix et du Marais, Paris, France). Ketamine or placebo were administered as an intravenous bolus after induction of anesthesia and before the surgical incision by the anesthetist in charge of the patient. Decisions about anesthetic technique were at the discretion of each anesthetic team. The only exception was the instruction to physicians not to administer any ketamine during surgery. All other aspects of patient care (including postoperative pain management) followed local protocols and established guidelines and all administered medications were collected.

Outcomes

The primary outcome was the proportion of objective delayed neurocognitive recovery (dNR) on postoperative day 7. While no consensus has been established regarding the timing of cognitive assessments after surgery, several studies have suggested an optimal timing at one week and three months post procedure, depending on the clinical picture and in the absence of confounding factors[3,19,20]. Thus, patients were assessed face-to-face by members of the research team,

specifically trained in cognitive assessment techniques, blinded to group assignment, using the MoCA test [18] and Trail Making Test (TMT) A and B, a validated tool to measure working memory (TMT A) and central executive functioning (TMT B) [21]. These assessments were administered based on a well-structured protocol to ensure the reproducibility of results across all participants. For each patient, the degree of deviation from the normative values of the reference population in France with a comparable mean age [22] was estimated as a Z-score (Z-score = $(x-\mu)/\sigma$, where x is the patient's raw score, μ is the reference population mean, and σ is the reference population standard deviation) for each cognitive test. An absolute difference of Z-score ≥ 1 in at least one cognitive test (MoCA or TMT A or TMT B or TMT B-A) between the tests carried out before surgery and seven days after surgery, defined objective dNR [4], aligning the objective criteria of perioperative cognitive disorders as described in DSM-5[23].

Secondary outcomes included the incidence of delirium assessed by trained members of the research team using the Confusion Assessment Method (CAM) algorithm twice daily from two hours after the end of surgery to postoperative day 7 [24]; the incidence of anxiety (defined as a anxiety score of 8 or above) and symptoms of depression (defined as a depression score of 8 or above) using the Hospital and Anxiety Depression Scale (HADS) at postoperative day 7 and three months after surgery – these cut-off values allowed to maximise combined HADS sensitivity and specificity and to identify people with higher symptom levels [25]; the proportion of objective postoperative neurocognitive disorder (POND) assessed by the same cognitive tests (MoCA or TMT A or TMT B or TMT B-A) three months after surgery at the surgical follow-up visit. Apathy was assessed using the Starkstein Apathy Scale at postoperative day 7 and three months after surgery and was defined as a score of 14 or above. Pre- and postoperative pain was assessed by a patient-reported Visual Analog Scale (VAS) at rest, from two hours after the end of surgery to postoperative day 7 on a daily basis and three months after surgery; cumulative opioid requirements were measured from postoperative day 0 to day 7 and the occurrence of neuropathic pain was measured three months after surgery using the DN4 score [26]. Psychiatric events, such as visual and auditory hallucinations, but not nightmares, were also collected after the end of surgery to postoperative day 7.

In the original design of the study, the primary endpoint was the incidence of delirium, and the study was powered to detect a relative decrease of 35%, i.e., a proportion of 13% of delirium in the ketamine group *versus* 20% in the placebo group. Considering the results of Avidan et al., which showed no difference between ketamine and placebo groups in terms of delirium incidence in similar settings to the POCK study, and those from the Hovaguimian meta-analysis highlighting a potential ketamine protection towards POCD [13,14], the POCK scientific committee decided to amend the study on 02/19/2018 with 93 patients already enrolled. The outcomes were modified as follows: the proportion of delirium was defined as a secondary outcome while dNR on postoperative day 7, which was initially a secondary outcome, was defined as the primary one. The protocol, including the stratification factors, underwent no other modifications, ensuring the study's consistency and integrity throughout its course. These modifications were approved in April 2019 by an institutional review board (Comité de Protection des Personnes Ile de France III, France) and registered in May 2019 (clinicaltrial.gov NCT02892916) when 301 patients had been recruited to the study. See more information in the Table S3. No interim analysis has been planned or performed.

Sample size calculation

We estimated a 33% incidence of the primary endpoint in the placebo group[27,28], and we assumed a relative decrease of 48.5%, i.e., a proportion of 17% in the ketamine group[13]. We calculated that 114 patients were required in each group with a two-sided type I error rate of 5% and a power of 80%. Due to the difficulties of administering the cognitive questionnaires at seven days after surgery, we estimated 20% missing values for completion of the questionnaire distributed on day 7 and therefore planned to randomize 274 patients.

Statistical analyses

The intention-to-treat (ITT) population consisted of all randomized patients and was used for patient-count purposes. The modified intention-to-treat (mITT) population comprised all randomized patients who received any cognitive assessment within the seven days following surgery. All analyses were performed on a modified intention-to-treat (mITT) basis. An additional per-protocol (PP) analysis was performed, including patients who received the randomly assigned treatment, adhered to the protocol-mandated medical treatment, and had no major protocol violations.

Clinical event rates and other categorical data are summarized as percentages. Continuous data are presented as means with standard deviations for normally distributed variables and as medians, interquartile range (IQR) with minimum and maximum values for variables not normally distributed. A two-sided P value of ≤ 0.05 was considered significant. Binary outcomes were analyzed using a logistic regression and results are presented as odds ratio (OR) with a 95% confidence interval (CI). Continuous variables were analyzed using a linear regression and results are presented using the estimates (standard error [SE]). Assumption of the model was assessed by plotting the residuals. VAS scores were analyzed using a continuous ordinal model with a logit link function and results are presented as ORs with 95% CI. In the latter analysis, an OR greater than 1 meant that patients with ketamine had higher odds of having less rather than more pain, compared to patients in the placebo group. All models were adjusted on the MoCA score (less than 20 (severe cognitive impairment), between 20 and 26 (MCI) and greater than 26 (considered normal)) at baseline and on age (< 70 years *versus* $\geq$ 70 years). Models for analyses of score and pain were also adjusted on the value at baseline. Predictive factors of cognitive decline on postoperative day 7 were determined by first performing a univariate analysis of known factors. Factors with a p-value < 0.15 were then included in the multivariate model.

Planned sub-group analyses of the primary outcome were performed according to age (< 70 years *versus* $\geq$70 years) and to the preoperative MoCA score (<26 *versus* $\geq$ 26).

Analyses were performed using SAS software, version 9.2 (SAS Institute, North Carolina, USA) and R statistical software version 4.0.2 (R Core Team, Vienna, Austria).

Results

Organization and reporting of this study followed CONSORT guidelines for randomized trials[29]. Between March 20, 2017 and May 28, 2019, 301 patients were randomly assigned, among whom 9 patients withdrew consent (Figure 1). The intention-to-treat (ITT) population included 292 patients, 149 in the ketamine group and 143 in the placebo group. Thirty-one (10.6%) patients (ketamine group, n=20; placebo group, n=11) did not receive any cognitive assessment within the seven days following surgery (mITT population: ketamine group, n=129; placebo group, n=132). The median number of included patients per site was 9.5 (range, 2 to 81) (Table S2). Twenty-six patients had protocol violations (did not undergo surgery (n=1), presented violations of inclusion criteria (n=3), did not receive study drug (n=3), received open-label ketamine in the placebo group (n=19)) and were excluded from the PP cohort.

Patient characteristics and types of surgical procedures did not differ between the two groups, nor did preoperative cognitive, anxiety, and symptoms of depression status (Table 1).

Primary outcome

In the mITT population, objective delayed neurocognitive recovery (dNR) on postoperative day 7 occurred in 50 (38.8%) patients in the ketamine group and 54 (40.9%) patients in the placebo group (OR [95% CI] 0.92 [0.56;1.51], p=0.73) (Table 2). The detailed results of the MoCA test, including results in each MoCA component [18] , and TMT A and B are reported in Tables S4 and S5.

Secondary outcomes

The rates of delirium during the initial seven postoperative days and objective postoperative neurocognitive disorder (POND) at three months did not differ statistically between the ketamine and placebo groups. The rates of anxiety, apathy, and fatigue were also comparable between the two

groups, both at seven days and three months after surgery. Symptoms of depression were significantly less frequent in the ketamine group at three months but not at day 7, in comparison to the placebo group (OR [95%CI] 0.34 [0.13-0.86]) (Table 2).

Pain at rest was decreased in the post-anesthesia recovery unit (PACU) in the ketamine group, but there was no statistical difference in acute pain intensity, postoperative consumption, and neuropathic pain at any tested timepoints (Tables S6 and S7).

High level of education was the only independent protective factor against objective dNR on postoperative day 7 (OR [95%CI] 0.41 [0.19;0.89]) (Table S8).

Per-protocol analysis

In the PP population objective dNR occurred in 50 (38.8%) patients in the ketamine group and 47 (41.6%) patients in the placebo group (OR [95% CI] 0.89 [0.53;1.49], p=0.65) on postoperative day 7.

The absence of effect of ketamine on the incidence of objective dNR on postoperative day 7 was consistent across all predetermined subgroups, i.e. preoperative cognitive status defined by the MoCA score (less than 20, between 20 and 26, and 26 or greater) and age (> 70 years *versus* ≤ 70 years) groups (Figure 2).

Safety

There was no statistical difference between the two groups in the rates of perioperative adverse events (34 [23.4%] in the placebo group *versus* 33 [23.1%] the ketamine cohort; OR [95% CI] 1.03 [0.59-1.78]) and in the postoperative psychiatric adverse events during the initial seven days following surgery (4 (2.68%) of 149 in the ketamine group and 5 (3.5%) of 143 in the placebo group; OR [95% CI] 0.76 [0.20; 2.92]).

Discussion

The POCK multicenter, randomized, placebo-controlled, double-blind trial, shows that the administration of 0.5 mg/kg single dose of ketamine before surgery is well-tolerated but does not reduce the occurrence of objective dNR at 7 days or objective POND at 3 months, nor does it reduce delirium, anxiety, apathy, chronic pain, and fatigue. However, it might reduce the rate of symptoms of depression at three months after surgery. Our results are in conflict with the conclusion of a recent meta-analysis, which concluded that an NMDA receptor antagonist such as ketamine improved cognition one week after surgery[13]. However, this meta-analysis was based on relatively small trials involving fewer than 60 patients. It is well known that large effectiveness trials do not always confirm the results from underpowered studies or meta-analyses. Furthermore, the major weight of its conclusions derives from one study conducted in cardiac surgery and it is likely that the mechanisms of postoperative cognitive impairment are different after cardiac and orthopedic procedures[30]. It must be emphasized that we have not restricted our trial to patients without pre-existing neurocognitive disorder, in contrast to previous studies[30]. Survey studies have shown that up to 35–50% of elderly patients aged ≥65 years have MCI[31] and preliminary findings suggest that surgery worsens attention/concentration in patients with this impairment[32]. The POCK trial does not confirm a higher impact of ketamine on objective dNR on postoperative day 7 in this specific population (i.e., MoCA < 26).

Our trial was based on the hypothesis that postoperative cognitive disorders are mainly a result of microglial activation, a key component of the neuroinflammatory process. Indeed, ketamine has been reported to tone down the neuroinflammatory process associated with surgery by reducing both pain and glutamate excitotoxic effects on microglial brain cells [9,33]. However, the current literature suggests that other factors might significantly contribute to postoperative cognitive disorders, including neurotransmitter imbalances [34] and oxidative stress [35]. Despite focusing on a homogeneous field of surgery, i.e. orthopedic surgery, immune stress induced by the surgery could vary based on the site of operation, whether it be the spine, shoulder, hip, or knee [36]. Additionally,

ketamine's effect on modulating microglial cells might have been insufficient. Based on previous published clinical trials in the field of perioperative cognition, the regimen of ketamine administration was a single preoperative low dose [14]. It must be noted that many interventional trials published on ketamine vary in terms of dosage (from 0.2 to 3 mg/kg) and duration of infusion (single bolus to 24-hour infusion) depending on the study main objective. No dose-effects have been described for ketamine, either in the prevention of acute and chronic pain management, depression, or postoperative delirium [37–40], leaving this question open. Interestingly, an infusion of ketamine of 0.2 mg/kg per hour has been shown to reduce ICU-associated delirium, whose main mechanism is also neuroinflammation [41], underscoring the potential value of ketamine in reducing both delirium and hyperalgesia, ultimately improving patient-centered outcomes such as quality of life in the ICU setting [42]. Moreover, it must be noted that our drug dosage was insufficient to obtain any major benefit of ketamine, i.e., a significant reduction of acute and chronic postoperative pain[43]. Pain is one of the mechanisms that could be involved in the occurrence of POND [44] and its chronicization has been associated with neuroinflammation[45]. In the POCK study, good pain control was shown in both groups, meaning that pain could not be considered as playing a significant role in POND incidence, lowering the potential impact of ketamine pain induced neuroinflammation. Notably, 35% of the POCK patients received locoregional or epidural anesthesia in conjunction with general anesthesia. However, this approach was not identified as a protective factor against postoperative neurocognitive disorders. This finding is consistent with a recent meta-analysis demonstrating that combined epidural-general anaesthesia did not significantly affect the incidence of such outcomes in patients undergoing non-cardiac surgery [46]. Altogether, we think that our study suggests that modulation of microglial cells is challenging – as this is also highlighted by trials on dexamethasone [47] – rather than that it rules out neuroinflammation as a mechanism of postoperative cognitive disorder[48]. Indeed, we have not specifically assessed microglial activation as it requires multiple, technically complex approaches, ranging from high-field magnetic resonance imaging (MRI) to positron emission tomography (PET) with translocator protein-18 kDa ligands. These techniques have been used to demonstrate a microglial role in Alzheimer’s disease[49] and postoperative cognitive dysfunction[50]. It is conceivable that administration of ketamine, not only before surgery but during and after, could better

target the neuroinflammatory process, as the immune systemic response to surgery is time sensitive and involves several mediators[51,52].

One of the secondary outcomes was the incidence of postoperative delirium. While a 5.1% incidence is less than expected in such a cohort of patients, especially when compared to that of 19.6% in the study by Avidan et al. [14] who used the Confusion Assessment Method as we did, this frequency is close to that of other recent trials in Asia[53]. Delirium incidences vary based on many risk factors, demographics including ethnic groups, or definitions [54]. The POCK investigators were especially instructed to diagnose delirium twice a day during the postoperative course. However, the objective cognitive function tests employed to evaluate inattention as part of CAM were not monitored, which is known to contribute to the under-recognition of postoperative delirium [55]. However, our results are in line with the Prevention of Delirium and Complications Associated with Surgical Treatments (PODCAST) trial results, which reported that ketamine 0.5 mg/kg and 1 mg/kg failed to prevent postoperative delirium[14].

Ultimately, one of the secondary outcomes studied here suggests that ketamine may decrease the rate of symptoms of depression three months after surgery, though this finding requires further investigation. The development of depressive symptoms is a common complication of major surgery and is independently associated with an increased risk of cognitive dysfunction. Over the past two decades, numerous randomized controlled trials have demonstrated the antidepressant effects of ketamine[56,57]. A recent meta-analysis supports intravenous ketamine administration for treating early depressive symptoms after surgery[58]. Beside modulation of neuroinflammation, the proposed mechanisms for these antidepressant effects include hippocampal neurogenesis enhancement, re-equilibration of glutamate release, and reversal of stress-induced synaptic deficits that may have long term consequences[59]. Of note, we defined symptoms of depression using HADS cut-off values to maximize combined HADS sensitivity and specificity and to identify people with higher symptom levels [25] . Consequently, this point deserves further investigation to be confirmed.

We acknowledge that the POCK study has several limitations. First, it was designed to define cognitive decline using a combination of psychometric assessments (TMT A and B) and screening tools (MoCA), as was proposed in most clinical trials at the time of our trial design (i.e., 2015). In 2018, two years after the first inclusions in the POCK study, the International Perioperative Cognition Nomenclature Working Group recommended the use of psychometric assessments that objectively assess specific cognitive domains such as the TMT A and B, rather than screening tools like the MoCA for the diagnosis of POND. Furthermore, they emphasized the importance of considering subjective complaints and Instrumental Activities of Daily Living (ADLs) in these assessments, components that were not monitored in our study [4]. However, the rate of 39.8% cognitive decline on postoperative day 7 is within the reported ranges, indicating that detection of cognitive dysfunction has been satisfactory in this study [3,60]. Second, although the POCK study included over 300 patients, it was designed with the prediction of a 48.5% relative decrease of POND in the ketamine group based on previous smaller studies. Even though there was an estimated lack of clinically meaningful (2.1%) and statistically significant (p=0.73) decrease in objective dNR incidence with ketamine, this could be a false negative finding. If ketamine does prevent postoperative cognitive decline, it is likely that the effect is small, and a large trial (e.g., > 10,000 patients per group) would be needed to clarify the effect. Third, we considered that it was clinically relevant to include patients with MCI or dementia (40% of our population), as they form a large part of those undergoing routine surgery. However, it is likely that the cognitive tests (MoCA or TMT A and B) are insufficiently sensitive for detecting changes in cognition in this specific population[61]. Fourth, actors that could contribute to the development of POND, such as pre-medication with anticholinergics or depth of sedation (low BIS values or RS), were not collected due to the complexity of the protocol. This may limit our ability to evaluate their potential causality in the incidence of cognitive disorders [62,63]. Finally, the ketamine used in our trial is a racemic mixture of two isomers. One may argue that administration of the levogyre form S-ketamine would have been more appropriate as it is considered to have more affinity for the NMDA receptor [64].

Conclusion

In conclusion, this randomized, multicenter, controlled, double-blind trial did not show that a preoperative 0.5 mg/kg intravenous single dose of ketamine improves cognitive outcomes, whether acute or long-term, in the elderly patient undergoing orthopedic surgery.

Consortium

The POCK Trial Investigators (in alphabetical order): Julie Bellet, Lucillia Bezu, Laetitia Bosch, Marine Coroir, Charles Coudriou, Philippe Cuvillon, Hervé Dezeque, Lucas Dreyfuss, Clément Gakuba, Fanny Garnier, Nadine Gengenwin, Pauline Glasman, David Joganah, Julien Josserand, Elsa Jozefowicz, Pierre Lambert, Denis Lemesle, Sabrina Ma, Gérard Macouillard, Rémi Menut, Eric Noll, Emmanuel Rineau, Emmanuel Samson, Danielle Saurel, Stefan Skwirba, Benoît Tavernier, Franck Verdonk.

Contributors

FV, TS, RG and JM designed the trial protocol. FV and JM lead the trial. All authors contributed to the data collection. ACN did the statistical analysis. FV was responsible for writing the draft of the manuscript with assistance from TS, SM and RG. All authors read, provided input, and approved the final manuscript. FV and ACN accessed and verified the data. All authors had access to the summarized data but not patient-specific data or group coding to maintain integrity of the trial. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Conflicts of Interest

The authors declare no competing interests.

References

[1] Meara JG, Leather AJM, Hagander L, Alkire BC, Alonso N, Ameh EA, et al. Global Surgery 2030: Evidence and solutions for achieving health, welfare, and economic development. The Lancet 2015. https://doi.org/10.1016/S0140-6736(15)60160-X.

[2] McDonagh DL, Mathew JP, White WD, Phillips-Bute B, Laskowitz DT, Podgoreanu M V., et al. Cognitive function after major noncardiac surgery, apolipoprotein E4 genotype, and biomarkers of brain injury. Anesthesiology 2010;112:852–9. https://doi.org/10.1097/ALN.0b013e3181d31fd7.

[3] Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. Lancet 1998;351:857–61.

[4] Evered L, Silbert B, Knopman DS, Scott DA, DeKosky ST, Rasmussen LS, et al. Recommendations for the nomenclature of Cognitive change associated with anaesthesia and surgery-2018. Anesthesiology 2018;129:872–9. https://doi.org/10.1097/ALN.0000000000002334.

[5] Steinmetz J, Christensen KB, Lund T, Lohse N, Rasmussen LS, ISPOCD Group. Long-term Consequences of Postoperative Cognitive Dysfunction. Anesthesiology 2009;110:548–55. https://doi.org/10.1097/ALN.0b013e318195b569.

[6] Boone MD, Sites B, Von Recklinghausen FM, Mueller A, Taenzer AH, Shaefi S. Economic Burden of Postoperative Neurocognitive Disorders among US Medicare Patients. JAMA Netw Open 2020. https://doi.org/10.1001/jamanetworkopen.2020.8931.

[7] Vacas S, Cole DJ, Cannesson M. Cognitive Decline Associated with Anesthesia and Surgery in Older Patients. JAMA - Journal of the American Medical Association 2021. https://doi.org/10.1001/jama.2021.4773.

[8] Alam A, Hana Z, Jin Z, Suen KC, Ma D. Surgery, neuroinflammation and cognitive impairment. EBioMedicine 2018;37:547–56. https://doi.org/10.1016/j.ebiom.2018.10.021.

[9] Verdonk F, Petit AC, Abdel-Ahad P, Vinckier F, Jouvion G, de Maricourt P, et al. Microglial production of quinolinic acid as a target and a biomarker of the antidepressant effect of ketamine. Brain Behav Immun 2019;81:361–73. https://doi.org/10.1016/j.bbi.2019.06.033.

[10] Dale O, Somogyi AA, Li Y, Sullivan T, Shavit Y. Does intraoperative ketamine attenuate inflammatory reactivity following surgery? A systematic review and meta-analysis. Anesth Analg 2012;115:934–43. https://doi.org/10.1213/ANE.0B013E3182662E30.

[11] Gitlin J, Chamadia S, Locascio JJ, Ethridge BR, Pedemonte JC, Hahm EY, et al. Dissociative and analgesic properties of ketamine are independent. Anesthesiology 2020;133:1021–8. https://doi.org/10.1097/ALN.0000000000003529.

[12] Kappelmann N, Lewis G, Dantzer R, Jones PB, Khandaker GM. Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. Mol Psychiatry 2018;23:335–43. https://doi.org/10.1038/mp.2016.167.

[13] Hovaguimian F, Tschopp C, Beck-Schimmer B, Puhan M. Intraoperative ketamine administration to prevent delirium or postoperative cognitive dysfunction: A systematic review and meta-analysis. Acta Anaesthesiol Scand 2018;62:1182–93. https://doi.org/10.1111/aas.13168.

[14] Avidan MS, Maybrier HR, Abdallah A Ben, Jacobsohn E, Vlisides PE, Pryor KO, et al. Intraoperative ketamine for prevention of postoperative delirium or pain after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial. The Lancet 2017;390:267–75. https://doi.org/10.1016/S0140-6736(17)31467-8.
[15] Daiello LA, Racine AM, Yun Gou R, Marcantonio ER, Xie Z, Kunze LJ, et al. Postoperative Delirium and Postoperative Cognitive Dysfunction: Overlap and Divergence. Anesthesiology 2019;131:477–91. https://doi.org/10.1097/ALN.0000000000002729.
[16] Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. The Lancet 2014;383:911–22. https://doi.org/10.1016/S0140-6736(13)60688-1.
[17] Silbert B, Evered L, Scott DA, McMahon S, Choong P, Ames D, et al. Preexisting cognitive impairment is associated with postoperative cognitive dysfunction after hip joint replacement surgery. Anesthesiology 2015;122:1224–34. https://doi.org/10.1097/ALN.0000000000000671.
[18] Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA : A Brief Screening Tool for Mild Cognitive Impairment. J Am Geriatr Soc 2005;53:695–9. https://doi.org/10.1111/j.1532-5415.2005.53221.x.
[19] Monk TG, Weldon BC, Garvan CW, Dede DE, van der Aa MT, Heilman KM, et al. Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology 2008;108:18–30. https://doi.org/10.1097/01.anes.0000296071.19434.1e.
[20] Needham MJ, Webb CE, Bryden DC. Postoperative cognitive dysfunction and dementia: what we need to know and do. BJA: British Journal of Anaesthesia 2017;119:i115–25. https://doi.org/10.1093/BJA/AEX354.
[21] Bowie CR, Harvey PD. Administration and interpretation of the Trail Making Test. Nature Protocols 2006 1:5 2006;1:2277–81. https://doi.org/10.1038/nprot.2006.390.
[22] Godefroy O, Groupe de réflexion sur l'évaluation des fonctions exécutives. Fonctions exécutives et pathologies neurologiques et psychiatriques : évaluation en pratique clinique 2008:312.
[23] Bowles T. Book Review: Diagnostic and statistical manual of mental disorders, fifth edition. Mental Health Clinician 2013. https://doi.org/10.9740/mhc.n163617.
[24] Hamadnalla H, Sessler DI, Troianos CA, Fang J, Rivas E, Ma C, et al. Optimal interval and duration of CAM-ICU assessments for delirium detection after cardiac surgery. J Clin Anesth 2021;71. https://doi.org/10.1016/J.JCLINANE.2021.110233.
[25] Wu Y, Levis B, Sun Y, He C, Krishnan A, Neupane D, et al. Accuracy of the Hospital Anxiety and Depression Scale Depression subscale (HADS-D) to screen for major depression: systematic review and individual participant data meta-analysis. The BMJ 2021;373. https://doi.org/10.1136/BMJ.N972.
[26] Attal N, Bouhassira D, Baron R. Diagnosis and assessment of neuropathic pain through questionnaires. Lancet Neurol 2018;17:456–66. https://doi.org/10.1016/S1474-4422(18)30071-1.
[27] Newman S, Stygall J, Hirani S, Shaefi S, Maze M. Postoperative cognitive dysfunction after noncardiac surgery: A systematic review. Anesthesiology 2007;106:572–90. https://doi.org/10.1097/00000542-200703000-00023.
[28] Rundshagen I. Postoperative cognitive dysfunction. Dtsch Arztebl Int 2014;111:119–25. https://doi.org/10.3238/arztebl.2014.0119.
[29] Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: Updated guidelines for reporting parallel group randomised trials. BMJ (Online) 2010;340:698–702. https://doi.org/10.1136/bmj.c332.

[30] Hudetz JA, Patterson KM, Iqbal Z, Gandhi SD, Byrne AJ, Hudetz AG, et al. Ketamine Attenuates Delirium After Cardiac Surgery With Cardiopulmonary Bypass. J Cardiothorac Vasc Anesth 2009;23:651–7. https://doi.org/10.1053/j.jvca.2008.12.021.
[31] Kapoor P, Chen L, Saripella A, Waseem R, Nagappa M, Wong J, et al. Prevalence of preoperative cognitive impairment in older surgical patients.: A systematic review and meta-analysis. J Clin Anesth 2022;76. https://doi.org/10.1016/J.JCLINANE.2021.110574.
[32] Bekker A, Lee C, de Santi S, Pirraglia E, Zaslavsky A, Farber S, et al. Does mild cognitive impairment increase the risk of developing postoperative cognitive dysfunction? Am J Surg 2010;199:782. https://doi.org/10.1016/J.AMJSURG.2009.07.042.
[33] Zhang N, Yao L, Wang P, Liu Z. Immunoregulation and antidepressant effect of ketamine. Transl Neurosci 2021;12:218–36. https://doi.org/10.1515/TNSCI-2020-0167.
[34] Naicker P, Anoopkumar-Dukie S, Grant GD, Neumann DL, Kavanagh JJ. Central cholinergic pathway involvement in the regulation of pupil diameter, blink rate and cognitive function. Neuroscience 2016;334:180–90. https://doi.org/10.1016/J.NEUROSCIENCE.2016.08.009.
[35] Netto MB, de Oliveira Junior AN, Goldim M, Mathias K, Fileti ME, da Rosa N, et al. Oxidative stress and mitochondrial dysfunction contributes to postoperative cognitive dysfunction in elderly rats. Brain Behav Immun 2018;73:661–9. https://doi.org/10.1016/J.BBI.2018.07.016.
[36] Dean MC, Cherian NJ, Eberlin CT, Rudisill SS, LaPorte ZL, Kucharik MP, et al. Total shoulder vs. hip and knee arthroplasty: an analysis of perioperative outcomes. Seminars in Arthroplasty JSES 2023;33:627–36. https://doi.org/10.1053/j.sart.2023.06.011.
[37] Gao M, Rejaei D, Liu H. Ketamine use in current clinical practice. Acta Pharmacologica Sinica 2016 37:7 2016;37:865–72. https://doi.org/10.1038/aps.2016.5.
[38] Schwenk ES, Viscusi ER, Buvanendran A, Hurley RW, Wasan AD, Narouze S, et al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Acute Pain Management From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med 2018;43:456–66. https://doi.org/10.1097/AAP.0000000000000806.
[39] Loo C. Can we confidently use ketamine as a clinical treatment for depression? Lancet Psychiatry 2018;5:11–2. https://doi.org/10.1016/S2215-0366(17)30480-7.
[40] Hollinger A, Rüst CA, Riegger H, Gysi B, Tran F, Brügger J, et al. Ketamine vs. haloperidol for prevention of cognitive dysfunction and postoperative delirium: A phase IV multicentre randomised placebo-controlled double-blind clinical trial. J Clin Anesth 2021;68:110099. https://doi.org/10.1016/J.JCLINANE.2020.110099.
[41] Perbet S, Verdonk F, Godet T, Jabaudon M, Chartier C, Cayot S, et al. Low doses of ketamine reduce delirium but not opiate consumption in mechanically ventilated and sedated ICU patients: A randomised double-blind control trial. Anaesth Crit Care Pain Med 2018;37:589–95. https://doi.org/10.1016/J.ACCPM.2018.09.006.
[42] Hayhurst CJ, Farrin E, Hughes CG. The effect of ketamine on delirium and opioid-induced hyperalgesia in the Intensive Care Unit. Anaesth Crit Care Pain Med 2018;37:525–7. https://doi.org/10.1016/J.ACCPM.2018.11.001.
[43] Cohen SP, Bhatia A, Buvanendran A, Schwenk ES, Wasan AD, Hurley RW, et al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain From the American Society of Regional Anesthesia and Pain Medicine, the American

Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med 2018;43:521–46. https://doi.org/10.1097/AAP.0000000000000808.
[44] Higgins DM, Martin AM, Baker DG, Vasterling JJ, Risbrough V. The relationship between chronic pain and neurocognitive function: A systematic review. Clin J Pain 2018;34:262. https://doi.org/10.1097/AJP.0000000000000536.
[45] Ji RR, Nackley A, Huh Y, Terrando N, Maixner W. Neuroinflammation and Central Sensitization in Chronic and Widespread Pain. Anesthesiology 2018;129:343–66. https://doi.org/10.1097/ALN.0000000000002130.
[46] Teng IC, Sun CK, Ho CN, Wang LK, Lin YT, Chang YJ, et al. Impact of combined epidural anaesthesia/analgesia on postoperative cognitive impairment in patients receiving general anaesthesia: a meta-analysis of randomised controlled studies. Anaesth Crit Care Pain Med 2022;41. https://doi.org/10.1016/J.ACCPM.2022.101119.
[47] Ottens TH, Sauër AMC, Peelen LM, De Groot WJ, Buijsrogge MP, Bredée JJ, et al. Effects of dexamethasone on cognitive decline after cardiac surgery: a randomized clinical trial. Anesthesiology 2014;121:492–500. https://doi.org/10.1097/ALN.0000000000000336.
[48] Safavynia SA, Goldstein PA. The role of neuroinflammation in postoperative cognitive dysfunction: Moving from hypothesis to treatment. Front Psychiatry 2019;9:752. https://doi.org/10.3389/FPSYT.2018.00752/BIBTEX.
[49] Zhou R, Ji B, Kong Y, Qin L, Ren W, Guan Y, et al. PET Imaging of Neuroinflammation in Alzheimer's Disease. Front Immunol 2021;12:3750. https://doi.org/10.3389/FIMMU.2021.739130/BIBTEX.
[50] Forsberg A, Cervenka S, Jonsson Fagerlund M, Rasmussen LS, Zetterberg H, Erlandsson Harris H, et al. The immune response of the human brain to abdominal surgery. Ann Neurol 2017;81:572–82. https://doi.org/10.1002/ana.24909.
[51] Yang T, Velagapudi R, Terrando N. Neuroinflammation after surgery: from mechanisms to therapeutic targets. Nature Immunology 2020 21:11 2020;21:1319–26. https://doi.org/10.1038/s41590-020-00812-1.
[52] Verdonk F, Einhaus J, Tsai AS, Hedou J, Choisy B, Gaudilliere D, et al. Measuring the human immune response to surgery: multiomics for the prediction of postoperative outcomes. Curr Opin Crit Care 2021;27:717–25. https://doi.org/10.1097/MCC.0000000000000883.
[53] Li T, Li J, Yuan L, Wu J, Jiang C, Daniels J, et al. Effect of Regional vs General Anesthesia on Incidence of Postoperative Delirium in Older Patients Undergoing Hip Fracture Surgery: The RAGA Randomized Trial. JAMA 2022;327:50–8. https://doi.org/10.1001/JAMA.2021.22647.
[54] Wilson JE, Mart MF, Cunningham C, Shehabi Y, Girard TD, MacLullich AMJ, et al. Delirium. Nature Reviews Disease Primers 2020 6:1 2020;6:1–26. https://doi.org/10.1038/s41572-020-00223-4.
[55] Kai-Chung Wong E, Lee JY, Surendran AS, Nair K, Maestra N Della, Migliarini M, et al. Nursing perspectives on the confusion assessment method: a qualitative focus group study. Age Ageing 2018;47:880–6. https://doi.org/10.1093/AGEING/AFY107.
[56] McGirr A, Berlim MT, Bond DJ, Fleck MP, Yatham LN, Lam RW. A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. Psychol Med 2015;45:693–704. https://doi.org/10.1017/S0033291714001603.
[57] Murrough JW, Iosifescu D V., Chang LC, Al Jurdi RK, Green CE, Perez AM, et al. Antidepressant Efficacy of Ketamine in Treatment-Resistant Major Depression: A Two-Site Randomized Controlled Trial. American Journal of Psychiatry 2013;170:1134–42. https://doi.org/10.1176/appi.ajp.2013.13030392.

[58] Wang J, Sun Y, Ai P, Cui V, Shi H, An D, et al. The effect of intravenous ketamine on depressive symptoms after surgery: A systematic review. J Clin Anesth 2022;77. https://doi.org/10.1016/J.JCLINANE.2021.110631.
[59] Carboni E, Carta AR, Carboni E, Novelli A. Repurposing Ketamine in Depression and Related Disorders: Can This Enigmatic Drug Achieve Success? Front Neurosci 2021;15:469. https://doi.org/10.3389/FNINS.2021.657714/BIBTEX.
[60] McDonagh DL, Mathew JP, White WD, Phillips-Bute B, Laskowitz DT, Podgoreanu M V., et al. Cognitive function after major noncardiac surgery, apolipoprotein E4 genotype, and biomarkers of brain injury. Anesthesiology 2010;112:852–9. https://doi.org/10.1097/ALN.0B013E3181D31FD7.
[61] Phua AKS, Hiu SKW, Goh WK, Ikram MK, Venketasubramanian N, Tan BY, et al. Low Accuracy of Brief Cognitive Tests in Tracking Longitudinal Cognitive Decline in an Asian Elderly Cohort. J Alzheimers Dis 2018;62:409–16. https://doi.org/10.3233/JAD-170831.
[62] Rossi A, Burkhart C, Dell-Kuster S, Pollock BG, Strebel SP, Monsch AU, et al. Serum anticholinergic activity and postoperative cognitive dysfunction in elderly patients. Anesth Analg 2014;119:947–55. https://doi.org/10.1213/ANE.0000000000000390.
[63] Chan MTV, Cheng BCP, Lee TMC, Gin T. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. J Neurosurg Anesthesiol 2013;25:33–42. https://doi.org/10.1097/ANA.0B013E3182712FBA.
[64] Jelen LA, Young AH, Stone JM. Ketamine: A tale of two enantiomers. J Psychopharmacol 2021;35:109–23. https://doi.org/10.1177/0269881120959644.

Tables

Table 1

Characteristics		All groups (n=292)	Ketamine (n=149)	Placebo (n=143)
Sex	Female	180 (61.64%)	93 (62.42%)	87 (60.84%)
Age	Mean (SD)	72.27 (7.22)	72.26 (7.11)	72.29 (7.36)
Education *	University or higher	106 (37.46%)	52 (36.36%)	54 (38.57%)
	High school	132 (46.64%)	75 (52.45%)	57 (40.71%)
Charlson comorbidity index **	Median [IQR]	3 [2.25;4]	3 [2;4]	3 [3;5]
Obstructive sleep apnea **		37 (12.76%)	17 (11.56%)	20 (13.99%)
Hypertension **		176 (60.69%)	89 (60.54%)	87 (60.84%)
Current smoker **		10 (3.45%)	6 (4.08%)	4 (2.8%)
Preoperative anemia (Hb <13 g.dl (male), Hb <12 g.dl^{-1} (female)) **		18 (6.25%)	7 (4.79%)	11 (7.75%)
Type of surgery	Shoulder arthroplasty	7 (2.41%)	5 (3.4%)	2 (1.4%)
	Spine surgery	72 (24.83%)	34 (23.13%)	38 (26.57%)

	Total hip arthroplasty	102 (35.17%)	53 (36.05%)	49 (34.27%)
	Total knee arthroplasty	76 (26.21%)	34 (23.13%)	42 (29.37%)
	Revision total hip arthroplasty	16 (5.52%)	11 (7.48%)	5 (3.5%)
	Revision total knee arthroplasty	13 (4.48%)	6 (4.08%)	7 (4.9%)
	Other	6 (2.05%)	6 (4.08%)	0 (0%)
Type of anesthesia ****	General plus regional (i.e., epidural analgesia or nerve block)	100 (34.72%)	42 (28.97%)	58 (40.56%)
Cognitive, anxiety and depression status				
Mean Montreal Cognitive Assessment score	Median [IQR]	25 [22;27]	25 [22;27]	25 [22;27]
Montreal Cognitive Assessment score range	[20-26] (mild cognitive impairment)	166 (56.85%)	86 (57.72%)	80 (55.94%)
	<20 (severe cognitive impairment-	30 (10.27%)	15 (10.07%)	15 (10.49%)
Anxiety (HADS Anxiety score of		133 (49.26%)	66 (48.18%)	67 (50.38%)

8 or above) †			
Symptoms of depression (HADS Depression score of 8 or above) ††	49 (18.28%)	21 (15.44%)	28 (21.21%)

Patients' baseline characteristics.

HADS, Hospital Anxiety and Depression Scale; Hb, hemoglobin; IQR, interquartile range; SD, standard deviation

* Denominator is 283 for *all groups*, 143 for *ketamine* and 140 for *placebo* groups

** Denominator is 290 for *all groups*, 147 for *ketamine* and 143 for *placebo* groups

*** Denominator is 288 for *all groups*, 146 for *ketamine* and 142 for *placebo* groups

**** Denominator is 288 for *all groups*, 145 for *ketamine* and 143 for *placebo* groups

† Denominator is 270 for *all groups*, 137 for *ketamine* and 133 for *placebo* groups

†† Denominator is 268 for *all groups*, 136 for *ketamine* and 132 for *placebo* groups

Table 2

	Ketamine (n=149)	Placebo (n=143)	OR [95%CI]	P-value
PRIMARY OUTCOME				
Objective delayed neurocognitive recovery (7 days after surgery) *	50 (38.76%)	54 (40.91%)	0.92 [0.56-1.51]	0.733
PRESPECIFIED SECONDARY OUTCOMES				
Seven days following surgery				
Delirium (positive CAM) **	6 (4.14%)	9 (6.34%)	0.80 [0.26-2.47]	0.698
Anxiety (HADS Anxiety score of 8 or above) ***	53 (42.74%)	53 (41.41%)	0.95 [0.51-1.77]	0.882
Symptoms of depression (HADS Depression score of 8 or above) ***	19 (15.32%)	27 (21.09%)	0.71 [0.30-1.70]	0.441
Apathy (Starkstein Apathy	34 (28.1%)	39 (31.2%)	1.08 [0.55-	0.83

Scale of 14 or above) ****				2.12]	
				Estimate (se)	**P-value**
Fatigue (Brief Fatigue Inventory) *****	Mean (SD)	3.97 (2.27)	4.28 (2.21)	-0.04(0.25)	0.884
Ninety days following surgery					
		Ketamine (n=125)	**Placebo (n=115)**	**OR [95%CI]**	**P-value**
Postoperative neurocognitive disorders †		26 (20.8%)	23 (20%)	1.05 [0.56-1.97]	0.884
Anxiety (HADS Anxiety score of 8 or above) ††		42 (33.87%)	42 (37.17%)	0.76 [0.41-1.39]	0.376
Symptoms of depression (HADS Depression score of 8 or above) ††		11 (8.87%)	24 (21.24%)	0.34 [0.13-0.86]	0.023
Apathy (Starkstein Apathy Scale of 14 or above) ††		36 (29.51%)	33 (29.73%)	1.40 [0.63-3.10]	0.404
				Estimate (se)	**P-value**

Fatigue (Brief Fatigue Inventory) †††	Mean (SD)	2.76 (2.03)	3.32 (2.08)	-0.41(0.23)	0.073

Cognitive and mood outcomes within the first 7 and 90 days following major orthopedic surgery in participants assigned to intra-operative ketamine or placebo groups.

Values are numbers.

CAM, Confusion Assessment Method; CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; OR, odds ratio; SD, standard deviation.

* Denominator is 129 for *ketamine* and 132 for *placebo* groups

** Denominator is 145 for *ketamine* and 142 for *placebo* groups

*** Denominator is 124 for *ketamine* and 128 for *placebo* groups

**** Denominator is 121 for *ketamine* and 125 for *placebo* groups

***** Denominator is 125 for *ketamine* and 129 for *placebo* groups

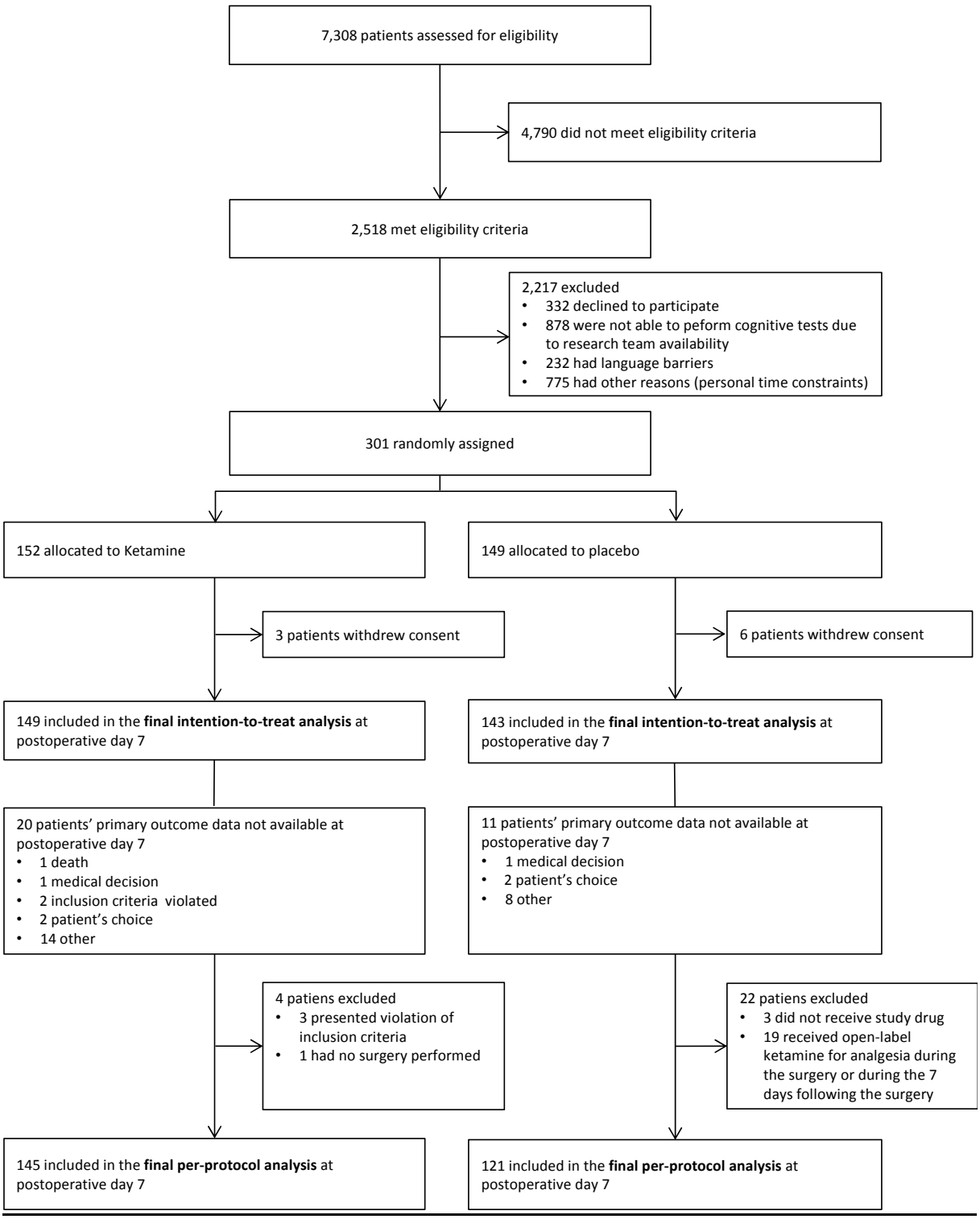
† Denominator is 125 for *ketamine* and 115 for *placebo* groups

†† Denominator is 124 for *ketamine* and 113 for *placebo* groups

††† Denominator is 124 for *ketamine* and 114 for *placebo* groups

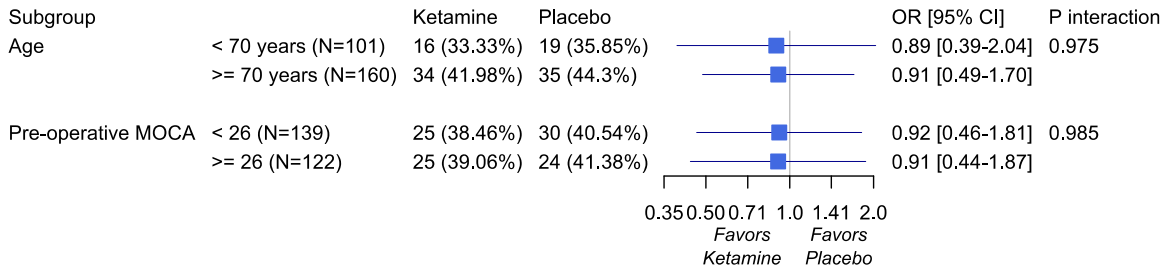
Figures

Figure 1



CONSORT flow diagram of participants

Figure 2



Subgroup analysis of objective neurocognitive recovery on postoperative day 7. Horizontal bars are 95% confidence intervals.